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MENINGOCOCCUS INFECTIONS INCLUDING MENINGITIS*

W. W. Herrick
Visiting Physician, Presbyterian and Sloane Hospitals

Any facts about an infection for which we have a satisfactory treatment have double value. Happily meningococcus infections are in this class. It may therefore be profitable to review such recent advance in knowledge of this disease as may be of value and at the same time to go over well established essential facts about it.

Because the meningococcus is an obligatory human parasite and does not infect lower animals under ordinary conditions, knowledge of this disease must be derived largely from the bedside. For this reason the clinician and pathologist are in position to speak with more authority than is the experimental worker.

Within recent years no facts of importance in regard to the bacteriology and immunology of this disease have been forthcoming. Authorities are still somewhat vague about the mechanism of immunity. Present opinion accords to phagocytosis and agglutination the most prominent place in this process. The organism has been found in almost every organ of the body. It has been repeatedly shown in the air passages throughout their entire extent; in the pleura, pericardium, peritoneum, circulating blood, endocardium, skin, joints, meninges, and middle ear. It has

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been associated with endocarditis, septicemia, meningitis, pneumonia, pleurisy, peritonitis, epididymitis, adrenal necrosis and hemorrhage, encephalitis, suppuration of the paranasal sinuses, tonsillitis and pharyngitis. Being one of the pyogenic cocci, it produces pus wherever it may lodge. In many of its clinical and laboratory properties, it is analogous to the pneumococcus. Like the pneumococcus the meningococcus is a variable species. It may be divided into definite groups or types with varying immunological properties. It may be that these groups are not fixed but vary in different epidemics and from time to time in a given epidemic, thus defying arbitrary classification. The recognition of this matter is of the utmost importance in the preparation and administration of anti-meningococcus serum.

One may conveniently and logically divide infections with this organism into three stages: The first, or carrier stage, is an involvement of the upper air passages. The oro- or nasopharynx, tonsils, and paranasal sinuses are singly or severally involved in every active case. This involvement is usually of short duration amounting to a few days. It may be followed by the other phases of the disease or the process may go no further.

There are chronic carriers who continuously or intermittently emit the meningococcus in the nasal discharge and sputum. These may be transitory, intermittent or permanent hosts of this micrococcus. These individuals keep the infection alive during non-epidemic periods. It is probable that the chronic carrier is himself immune to the infection.

The infection may not go beyond this first or carrier stage. This seems to be borne out by the observed frequency of mild infections of the upper respiratory tract in communities in which meningococcus infection is rife. Coryza, pharyngitis, sinusitis or tonsillitis with the diplococci obtainable sometimes in pure culture may occur as an isolated manifestation of this infection. The exudate in the nasopharynx and oropharynx is very viscid and

patches which may appear on lymphoid tissue are superficial and grayish, never very dense. In addition there is much local congestion. There may be a mild toxemia or no symptoms of importance.

The second stage of this infection is a bacteremia. Demonstration of this stage, which is the direct result of clinical studies made during the World War, has apparently solved the long debated question as to the avenue of transport of the diplococci from the upper air passages to the meninges. It may be said that the proof of a meningococcemia is ample and has been obtained under conditions of both military and civilian life. On the contrary, satisfactory volume of proof of the direct transmission of the infection from the nasopharynx or paranasal sinuses to the meninges is lacking. The clinical picture of meningococcemia is quite definite and may be readily recognized by the alert and experienced clinician. With or without the preliminary infection of the upper air passages, the patient suddenly becomes prostrated and febrile. The temperature in the average case is around 102. It may be subnormal. It may be very high. Frequently there is chill at onset. Of striking interest is the effect of the toxin on the higher centers. Patients are stupefied. The expression is characteristically blank. Replies are in monosyllables. Active delirium is rare. There is a tendency to lie quietly, to take little note of surroundings and to resent interference. Attempt at movement is resisted in a protesting querulous manner. Movement is painful. There is complaint of a general soreness and aching all over the body which may simulate acute polyarthritis. The skin gives us very valuable evidence at this stage of the disease. There is evidence of a vasomotor disturbance. Patients present a mottled pallor sometimes with a patchy suffusion of the face. There is a redness of the conjunctivæ. Tache cérébrale may be observed. Almost diagnostic is the hemorrhagic rash. Pathologically this consists of minute hemorrhages into the skin. Usually of pin-head size, these may reach a diameter of several inches or in fulminating cases amount

to a diffuse purpura. Like other hemorrhagic rashes, they do not disappear on pressure. They continue bright for two or three days when they fade leaving a rusty stain. Most commonly they occur about the shoulder and pelvic girdle; in more severe cases, over the trunk, conjunctivæ, mucosa, extremities or even the face. They come out very quickly and within one to two hours a patient previously without skin lesions may show an astounding number of these purpuric spots. From these the ancient term "spotted fever" arises. In some severe cases large hemorrhagic areas will undergo necrosis resulting in considerable and often deep destruction of skin and even of muscle. Such lesions are very suggestive of vascular thrombosis. At necropsy these hemorrhagic lesions are apparent on all the serous surfaces. They are undoubtedly the cause of the early arthralgia or arthritis so common in the septic stage of meningococcemia. In the more chronic cases, particularly the relapsing types without meningitis, one sees a maculo-papular roseola very like the rose spots of typhoid fever except in size. Many of these spots are one-half inch in diameter. They are most common on the trunk and appear in groups. Usually they are rather sparsely distributed. They have been mistaken for chicken pox, typhoid fever or erythema nodosum.

Among the laboratory findings in meningococcemia a high polymorphonuclear leucocytosis is almost constant. In no other disease excepting pneumonia is there such an early and marked leucocytosis. The pulse is rapid. The blood pressure is low. The meningococcus may be obtained from the upper air passages; from the blood stream by appropriate blood culture methods or on direct smear; from the skin lesions and even from the clear cerebrospinal fluid. If detailed proof of a meningococcemia were required, one might find it in the reports of positive blood cultures obtained in the stage of the disease under discussion. In an epidemic in the army in 1917-18 in 12 consecutive cases under my own study a positive blood culture was obtained in 10. McLean and Caffey reported 14 positive blood cul-

tures in a series of 17 cases in children. Smithburn et al. reported 63.8 per cent of positive blood cultures in 119 cases. McLean and Caffey obtained meningococci on smear from the hemorrhagic skin lesions of children. Symptoms of meningeal irritation may be entirely absent at this stage or they may occur simultaneously with it. In some epidemics the stage of meningococcemia has recognizable duration from a few hours to a few days before the development of meningitis.

The metastatic phase of meningococcus infections is the one with which most of us are familiar. The meninges are involved in at least 90 per cent of the cases. This may occur so early as to appear to be the initial process of the disease. However, in epidemics in which control of material is possible and study can be carried out from the onset of any symptoms whatsoever, conditions such as obtain in military camps, in hospitals, industrial or other organizations, the early phase of this infection can usually be detected. It is probable that epidemics differ and that in some, certain of the septic manifestations of the disease are not prominent.

It is not necessary to recount in detail the symptoms and signs of meningitis. The bursting headache, vomiting, the frequent delirium, the irritability, the stiff neck, and the findings on lumbar puncture are known to every clinician.

Of special interest is the prevalence and the picture of the disease in small infants. This has been studied especially by McLean. This observer found that in addition to the classical signs of meningitis, a failure to nurse properly, an excessive irritability, bulging fontanel, ophthalmoplegia, or a Cheyne-Stokes' respiration in infants make important the consideration of a meningococcus meningitis.

The spinal fluid presents certain well defined phases in this disease. In the stage of meningococcemia it is clear, contains a normal amount of cells and usually a few extra-

cellular isolated diplococci. These may be obtained on culture when they are not found on smear of the centrifugalized specimen. An increase in globulin and in cells follows soon. At first the cells are largely mononuclear in type, probably desquamated ependymal cells; later polymorphonuclears appear in quantity. In a few hours polymorphonuclear cells are from 90 to 100 per cent of the white cells present while fibrin, red blood cells and meningococci complete the picture. At first the organisms are largely or wholly without the cells but as the process matures they become intracellular in localization. With satisfactory response to serum therapy or a spontaneous recovery, the polymorphonuclear cells gradually give place to lymphocytes, organisms disappear, the fluid gradually becomes clearer and less in quantity. A condition of hypersecretion of the fluid and increased pressure in the subarachnoid system may last for some time after the fluid approaches the normal in all other respects.

Certain mechanical accidents of the disease are of importance. In the early stages of meningitis there may be a great increase in the bulk of the entire encephalon due not only to the meningeal exudate but also to extreme congestion and to an encephalitis which may be characterized by engorgement of the vessels, edema and a perivascular exudate. The not infrequent encephalitis of meningococcus infection has been little stressed. This lesion may take the form of localized hemorrhagic and purulent exudate in the brain substance and may well account for some of the persistent symptoms in cases not yielding to treatment. The result of an acute increase in the bulk of the encephalon may be a wedging of the brain stem in the foramen magnum. Clinically this is evidenced by intense engorgement of the face and veins of the forehead, bursting, agonizing headache, wild delirium, often with a slow pulse and other evidence of increased intracranial pressure. Sudden death may result. In addition to the specific therapy, management should be by venesection, by

the use of Epsom salts in the alimentary tract and by injections of glucose intravenously.

The subarachnoid system is an accessory circulation. The fluid courses from its point of origin in the choroid plexus through the foramen of Monro, the aqueduct of Sylvius, the fourth ventricle, thence through the foramina of Luschka and Magendie to the subarachnoid spaces covering the brain, cerebellum and cord. Absorption into the lymphatic stream is by the pacchionian bodies and the sheaths of the cranial nerves. In meningitis organized exudate may close this circuit at any point resulting in accumulation of fluid and distention of the ventricles or other subarachnoid spaces proximal to the point of occlusion. This condition is known as subarachnoid block. It most commonly occurs at the foramina of Luschka and Magendie, occasionally in the aqueduct, rarely in a foramen of Monro or about the cord. In some cases defective absorption from the entire drainage field may account for hydrocephalus without obvious local subarachnoid occlusion. This state may be combined with hypersecretion. The result of block is an acute hydrocephalus or hydrocephalic meningitis. The important symptoms are increase in meningeal irritation, obtunded mentality, an irregular, intermittent temperature, rapid trophic disturbance characterized by wasting so that the patient may become almost a living skeleton; evidence of increased intracranial pressure as shown by slow pulse and elevated blood pressure, sometimes by choking of the optic disk. At necropsy one finds great distention of the ventricles and flattening of the convolutions. If unrelieved, death is almost certain. In some cases in children a chronic hydrocephalus results.

Polyarthritis is a prominent symptom in the early stages. It is probably associated with hemorrhage into the joint membranes. It may be very acute and a source of bitter complaint. It is one of the factors that compels the patient to remain quiet and immobile. This type of arthritis is transitory and clears away with the hemorrhagic rash. Another type is a mono-arthritis, usually affecting the

knee, occasionally other large joints. It is characterized by purulent exudate in which meningococci can usually be found. It is subacute in its course, rather late in its appearance, is of good prognostic omen and, after a variable duration, clears away without leaving any disability. An interesting feature is the relatively painless character of this meningococcic mono-arthritis. Swelling and exudate may be great but spontaneous pain or pain on movement is very slight. Cases of this kind may occur without meningitis. A relatively painless arthritis of the larger joints in which the local features are more prominent than the symptoms and in which the course is prolonged and particularly when accompanied by a maculo-papular rash should bring into consideration a general infection with the meningococcus. Not infrequently cases of this type are called purpura rheumatica, a term which may give verbal satisfaction but which should never be accepted as a final diagnosis.

Pericarditis is not infrequent. It is of the sero-purulent or fibrino-purulent type. While a serious complication, it is not necessarily fatal. It may be attended by a large amount of exudate requiring paracentesis.

Endocarditis is very infrequent. It is of the vegetative type and may involve either side of the heart. It is practically always fatal.

Meningococcic pleurisy, while rare, may occur and offers about the same problem as meningococcic pericarditis. It is doubtful if the pneumonia often associated with meningococcic infections is due primarily to this organism. Peritonitis does occur although very rarely. Epididymitis is a factor in some epidemics. It is not a florid process. Cases seldom have any symptoms except the local swelling which in my experience subsides without subsequent atrophy.

The eye may play an important part in the symptomatology of this disease. In the initial stage conjunctivitis is a feature. In the bacteremic stage petechial spots of

varying size occur in the conjunctivæ. Strangely enough these are not found in the retina. Meningococcic panophthalmitis is one of the most disturbing symptoms of the disease. Careful observation of its onset does not suggest that the avenue of infection is by the optic nerve sheaths; rather does it seem to indicate that the infection is from the blood stream. An intense congestion of the vessels of the sclera with severe pain and increased tension is the first feature. Rapidly the media become cloudy. Then the eye becomes infiltrated with pus. The tension later falls and the eye is destroyed. In only one case, that reported by McLean and observed by myself at the Babies' Hospital, has there been recovery after this process had become established. In this case there was complete restoration of vision. Usually, however, the sight is destroyed and the eye requires enucleation. I have more than once seen this process affect both eyes. From experience I am sure that enucleation in these cases should be deferred until the process becomes well walled off and active sypmptoms of the disease have been absent for some weeks.

Of the cranial nerves the first is very rarely affected. Anosmia may rarely be observed. The ophthalmic nerve may give evidence of increased intracranial pressure in choked disk in later stages of the disease especially with hydrocephalus. Intense engorgement of the retinal veins and of the optic disk is not an infrequent feature of the early phases of this infection. The third nerve may show irritation or paralysis, giving rise to the strabismus which is so common in the meningitic phase. The sixth nerve owing to its long and exposed course at the base of the brain is very likely to show symptoms of irritation or paralysis. The fifth nerve apparently escapes injury in this disease. The facial nerve is not infrequently affected especially in children, giving rise to facial spasm or paresis. Affection of the eighth nerve is common. The deafness which results is unfortunately in almost all cases permanent. The remaining cranial nerves are not seriously affected unless we mention the bradycardia which is the

probable result of increased vagus stimulation from the rise of intracranial pressure. Cheyne-Stokes' or Biot's breathing may also have a similar origin.

COURSE

Few infections have a more variable course. Death may come with startling suddenness. Numerous instances of death four hours after onset have occurred. Abortive cases occur without the development of serious systemic or local symptoms. Typical cases may run their course for weeks. Relapses may occur so that the patient is afflicted for several months.

Factors in duration are the severity of the infection and the response to serotherapy. The prognosis in an individual case had best never be made. No one can give a satisfactory prediction of the outcome in a given case. Unfavorable features are great abruptness of onset with a high or subnormal temperature, great prostration, extensive hemorrhagic rash, polyarthritis or such complications as endocarditis, pericarditis, hydrocephalus, extensive cranial nerve involvement and particularly a lack of response to treatment with serum. Most important of all in prognosis is the promptness of diagnosis and treatment. If adequate amounts of suitable serum can be given within forty-eight hours of onset, the mortality should not be above 12 per cent. If the diagnosis is tardy and serum therapy deferred until later, the mortality tends to rise about 10 per cent for each twenty-four hours of delay.

Cases with a very low or a very high leucocyte count and with a very high percentage of polymorphonuclear cells are likely to do badly. Extensive purpura is a death warrant. Occasionally in grave cases the spinal fluid will show little or no cellular reaction but myriads of meningococci. Such are always fatal. Fortunately most cases that recover recover completely. A period of nervous and muscular asthenia, of intolerance of sunlight, of headache, may be observed. Rarely in children deaf mutism may result or chronic hydrocephalus with its mental and physical

symptoms. Blindness of central origin is likely to be transitory. When of peripheral origin it is permanent.

Treatment

Treatment is one of the most important chapters in medicine. Every practicing physician should have a clear picture of the early features of this disease and a well planned course of action in the event of its recognition.

Of the general treatment of meningococcus infections little need be said. Quiet is essential. Strong light should be avoided. Pain should be relieved by ample doses of opiates. The specific treatment should be carried out promptly and thoroughly. In this disease half way measures are not to be tolerated. In the early phases of the infection each hour counts and delay may incline the balance between life and death. Among experienced clinicians there is little debate about methods of serum therapy. When the diagnosis has been made early in the stage of bacteremia, it is obvious that intravenous therapy is required. Intravenous therapy is also valuable in the early stages of the metastatic or meningeal stage. Its advantages are that one can give a large volume of antibody. An argument of the opponents of intravenous therapy is that it is unnecessary since serum given intraspinally finds its way into the blood stream. While this is a fact, a fact of greater importance is that the amount of serum that can be given by the intraspinal route is limited. Rarely more than 35 c.c. can be administered intraspinally. Experience has shown that intravenous therapy to be effective must be a massive therapy, the average adult requiring doses of 100 c.c. of serum. A more valid argument in opposition to intravenous therapy is that reactions occur and are sometimes serious. This is true of any intravenous serum treatment. Despite all precautions, grave and even fatal accidents may occur occasionally. The patient, however, is in less danger from serum reactions than he is from an inadequately treated meningococcus infection. The lesser danger lies in thorough treatment.

The outline of the treatment of an average case of men-

ingococcus infection may be given. If the diagnosis is made within four days of onset or if petechial hemorrhage or other evidence of systemic infection is present, the average adult should receive 100 c.c. of antimeningococcic serum in the vein. This should be repeated in from six to eight hours if the condition is serious; in twelve to twenty-four hours if the symptoms appear to be under control. Usually three intravenous treatments are adequate. These should be given with every possible precaution against anaphylaxis. Sensitization of the skin should be determined beforehand. An injection of a small amount of serum should be given under the skin. If the patient seems sensitive, desensitization by increasing amounts of serum should be carried out. When administering serum the first 15 c.c. should be introduced at the rate of one c.c. a minute, observing the patient carefully for palpitation, dyspnœa, urticaria, precordial distress, collapse or other evidence of sensitiveness to serum. If this point in the serum administration is passed without serious effect, the rest of the treatment may be given without delay. Further intravenous serum treatments are very unlikely to result in distressing symptoms. Daily intraspinal treatments should be begun as soon as the spinal fluid becomes cloudy. Under ordinary conditions diagnosis is not made until this occurs. In patients whose symptoms are relatively mild, intraspinal treatments alone will suffice. However, if there is evidence of toxemia and of a severe infection, in my opinion, intravenous treatment should be used despite tardy recognition of the disease. The average case requires four to six intraspinal treatments. Some will need as many as twenty.

Fundamental in serotherapy of this disease is the use of a serum containing the antibodies specific for the type of meningococcus concerned. It must be thoroughly recognized that serums vary in their antibody content and that the meningococcus is not a fixed species. In the treatment of every case, therefore, we must recognize two variable

factors; the organism and the serum. Excepting the therapeutic effect there is no satisfactory way in which the efficacy of a serum can be measured. Next to the result of its administration to the patient, the agglutinin content is most reliable as a test of therapeutic efficacy. To be effective therapeutically the serum should agglutinate the organism obtained from the patient's air passages, circulating blood, skin or meninges in at least 1 in 50; better 1 in 800 or 1200.

If the response to serum is not prompt and effective, if the improvement in the patient's condition is not striking one must immediately discard the serum used and obtain some from another source in the hope that this second serum will contain the necessary antibodies. This is a fundamental rule of which no practitioner should be unaware.

The cause of continued symptoms must be sought in a number of directions. An overwhelming type of infection may be present in which case death is not long delayed. Treatment may have been inadequate or the serum used may not be adapted to the type of infection concerned. Some complication may have arisen. Those to be looked for are pneumonia, pericarditis, endocarditis, arthritis, epididymitis, subarachnoid block, encephalitis, cerebral or cerebellar abscess. After the seventh day serum sickness must be regarded as a possible cause of persistent symptoms. It is often difficult to decide when to stop treatment. Such a decision is important because it is quite possible to overdo treatment.

In the later phases of the disease one may meet a condition in which there is a slight irregular fever with other persistent symptoms and in which each intraspinal treatment is followed by an increased meningeal irritation. At this point careful study of the spinal fluid should be made. If organisms cannot be found on smear or culture, if lymphocytes are 10 or more per cent of the cells present in the fluid and if the cell count is lessening, one is usually

safe in considering that the infection is under control. In this event all serotherapy should be omitted. The spinal fluid should be withdrawn daily or on alternate days for careful study. If polymorphonuclear cells increase in number and proportion, if organisms reappear or if symptoms of infection do not abate, intraspinal treatment may be renewed cautiously. Usually, however, it is best to let nature take its course and the patient will promptly get well if let alone. In the later stages of the meningococcus meningitis, a hypersecretion of fluid may be annoying. There is persistent meningeal irritation with headache. Lumbar puncture obtains a large amount of fluid under considerable pressure. The fluid is not likely to be very cloudy and contains comparatively few cells and no organisms. In a case of this kind one should not give serum but should drain by the lumbar route if such drainage is followed by relief. The outlook is usually good in this situation.

Treatment of other metastatic purulent foci as in arthritis, pericarditis, etc., is by the withdrawal of pus and the local injection of meningococcus serum.

Treatment of the mechanical accidents of the disease is most important. If unrelieved, they are fatal. Cistern puncture is of great value in spinal subarachnoid block as it makes drainage effective and serum administration possible. This measure is also of use in the not infrequent block at the foramina of Luschka and Magendie. If block has occured higher up in the aqueduct of Sylvius or foramina of Monro, one must resort to ventricular puncture either through the fontanel in children or the corpus callosum in adults. One should not hesitate to establish this drainage. Serum may be administered into the ventricles at the same time. Radical surgical measures such as constant drainage are probably unwise. Recurrences are not infrequent, sometimes after an interval of several months. Necropsy studies have revealed that the typical exudate in the meninges is absorbed very slowly. This probably acts as a nidus of infection. To ward off recurrences it seems wise to give vaccines to the convalescent. One might sug-

gest one-half billion of killed meningococci subcutaneously at intervals of a week for three or four doses.

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